REMARKS

In this amendment, claim 35 has been amended. Support for the amendments to claim 35 can be found on page 4, lines 4-5 of the application as filed. No new matter has been added by way of these amendments.

Thus, with entry of this amendment, claims 15, 16, 35, 36, 40, and 41 remain pending and at issue.

Claim Rejection – 35 U.S.C. § 112, second paragraph

Claims 15-16 and 35 remain rejected under 35 U.S.C. §112, second paragraph, as being indefinite. According to the Examiner, claim 35 recites the phrase "detecting effectiveness of a skin treatment," but is it unclear how to do so because (a) it can not be presumed that basal CYP2S1 levels of adjacent samples are the same such that adjacent samples of treated and untreated skin can be compared and (b) if a sample of skin is taken from a patient suffering from a skin condition not associated with an increase or decrease in CYP2S1, the method yields a false negative.

Applicants respectfully traverse the indefiniteness rejection. Whilst one cannot be sure that the levels of CYP2S1 would be the same in adjacent locations of diseased skin, the skilled addressee would consider it reasonable and likely that they will be the same or comparable. The samples used for detecting CYP2S1 are destroyed when CYP2S1 levels are being measured. Thus, it is impossible to test the exact same sample before and after a skin treatment. The next best alternative, which is widely accepted, is to use adjacent skin for testing as recited in the claims. Moreover, Applicants have amended claim 35 to recite a method for assessing the ability of a skin treatment to modulate CYP2S1. Thus, the method will not yield a false negative since the ability of a skin treatment to modulate CYP2S1, as recited in the preamble, is explicitly being determined as set forth in the steps of the claims.

For at least these reasons, Applicants respectfully request withdrawal of the indefiniteness rejection.

Claim Rejection – 35 U.S.C. § 103

Claims 15-16, 35-36, and 40-41 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Bickers (Bickers *et al.*, *J Clin Invest* 1978, 62:1061-1068), Janmohamed (Janmohamed *et al.*, *Biochem Pharmacol* 2001, 62:777-786), Nelson (Nelson *et al.*, Arch *Biochem Biophys* 1999, 369:1-10), and Rylander (Rylander *et al.*, *Biochem Biophys Res Comm* 2001, 281:529-535). The Examiner assert that Bickers teaches a method for determining the effectiveness of coal tar as a skin treatment by measuring enzyme levels, but not including the levels of CYP2S1. According to the Examiner, Janmohamed discloses the expression of members of the CYP2 family in human skin and cites to Nelson which discloses a UNIGENE of CYP2S1. Rylander teaches, according to the Examiner, the isolation and cloning of CYP2S1, methods of detecting CYP2S1 using an antibody, and methods of measuring CYP2S1 mRNA.

The Examiner contends that it would have been obvious to one of ordinary skill in the art at the time of the invention to determine which of the CYP proteins disclosed by Nelson are expressed in the skin and to use the CYP2S1 of Rylander in the Bickers method. One would have been motivated to do so because CYP2S1 has been cloned to allow for easier and more specific detection of CYP2S1. There would have been a reasonable expectation of success because Janmohamed teaches expression of several CYP2 family proteins in the skin, Rylander teaches the sequence for CYP2S1 and how to detect CYP2S1, and Rylander and Janmohamed teach the well known technique of Northern blot analysis of the distribution of proteins in human tissue.

Applicants respectfully traverse the obviousness rejection.

Applicants discovered that CYP2S1 levels vary between diseased and non-diseased skin. This finding provides for the identification of skin treatments that modulate CYP2S1 levels in diseased skin as recited in claim 35 and for the detection of varying levels of CYP2S1 in diseased and non-diseased skin as set forth in claim 36. The present claims are not obvious because none of the cited references, alone or in combination, teach or suggest this discovery embodied by the claims.

Bickers merely teaches that one particular cytochrome P-450 dependent enzyme (AHH) is induced upon application of coal tar to the skin. As conceded by the Examiner, Bickers does not refer to the CYP2S1 enzyme. Rylander teaches the identification and tissue distribution of CYP2S1, but does not identify its expression in skin as required by the claims and certainly does not disclose the differential expression of CYP2S1 in normal versus diseased skin.

The Examiner previously rejected the claims as obvious over Bickers and Rylander, but has cited Nelson and Janmohamed as additional references in the obviousness rejection. These added references do not give merit to the obviousness rejection.

Nelson, as cited in Janmohamed, merely confirms that many cytochrome p450 enzymes have been identified, including CYP2S1, but there is no discussion of CYP2S1 being associated with any diseases, or indeed being expressed in the skin. Moreover, the Janmohamed disclosure on page 778, first column, although mentioning that cytochrome P450s are involved in extra-hepatic metabolism of drugs, points out that cytochrome P450 forms in human skin are limited. The rest of Janmohamed is only concerned with CYPs 2A6, 2B6 and 3A4 and importantly there is simply no mention whatsoever of CYP2S1, or its potential modulated expression in disease versus non-diseased skin as discovered by the present inventors.

Thus, Bickers, Janmohamed, Nelson, and Rylander, alone or in combination, do not disclose or suggest that CYP2S1 levels vary between diseased and non-diseased skin. Moreover, the Examiner has failed to provide a sufficient reason to combine the cited references especially since Janmohamed discloses that Cytochrome P450 forms in human skins are limited. One of ordinary skill in the art would be dissuaded from embarking on the "fishing" exercise as stated by the Examiner: "to determine which of the CYP proteins disclosed by Nelson et al. are expressed in the human skin." See page 7 of the Office Action. The Examiner has simply applied hindsight to the claims and mosaiced a number of documents, quite inappropriately, to contend that the claims are obvious.

Even if one were to combine the teachings of the cited references, there would be no expectation that a difference between the levels of CYP2S1 in diseased and undiseased skin as embodied by the claims would be observed. The furthest anyone could go with such teachings would be that CYP2S1 may be expressed in the skin and may be responsible for some degree of metabolizing drug substances applied to the skin. Thus, it is quite conceivable that CYP2S1 would not be expressed in skin tissue and would not be present in different levels in diseased and undiseased skin.

For at least these reasons, Applicants respectfully request withdrawal of the obviousness rejection.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered, that the amendment be entered, and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned.

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Respectfully submitted,

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